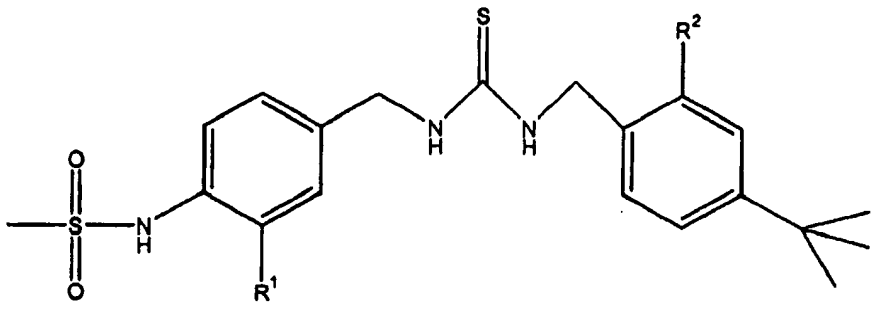
Claims

[1] A pharmaceutical composition comprising: a thiourea derivative of formula (I)



(I)

or a pharmaceutically acceptable salt thereof; and a cyclodextrin or its derivative, wherein,

R^1 is hydrogen, fluoro, chloro, methoxycarbonyl, carboxyl or hydroxyaminocarbonyl, and

R^2 is hydrogen, methoxy, ethoxy, propoxy, butoxy, isopropoxy, isobutoxy, neopentoxy, methoxymethoxy or benzyloxy.

[2] The pharmaceutical composition of claim 1, wherein the thiourea derivative is selected from the group consisting of:

1-(4-t-butylbenzyl)-3-(3-fluoro-4-methanesulfonylaminobenzyl)thiourea,

1-(4-t-butylbenzyl)-3-(3-chloro-4-methanesulfonylaminobenzyl)thiourea,

1-(4-t-butylbenzyl)-3-(3-methoxycarbonyl-4-methanesulfonyl-aminobenzyl)thiourea,

1-(4-t-butylbenzyl)-3-(4-methanesulfonylaminobenzyl)thiourea, and

1-(4-t-butyl-2-isobutoxybenzyl)-3-(4-methanesulfonylaminobenzyl) thiourea.

[3] The pharmaceutical composition of claim 1, wherein the thiourea derivative is 1-(4-t-butylbenzyl)-3-(3-fluoro-4-methanesulfonylaminobenzyl) thiourea.

[4] The pharmaceutical composition of claims 1 to 3, which comprises the cyclodextrin or its derivative in an amount ranging from 1 to 20 parts by weight per 1 part of the thiourea derivative or the pharmaceutically acceptable salt thereof.

[5] The pharmaceutical composition of claims 1 to 4, wherein the cyclodextrin is of α-, β- or γ-type.

[6] The pharmaceutical composition of claims 1 to 5, wherein the cyclodextrin derivative is selected from the group consisting of 2,6-dimethyl-β-cyclodextrin, 2-hydroxyethyl-β-cyclodextrin, 2-hydroxypropyl-β-cyclodextrin,

2-hydroxyethyl-γ-cyclodextrin, 2-hydroxypropyl-γ-cyclodextrin, (2-carboxymethoxy)propyl-β-cyclodextrin, and sulfobutylether-7-β-cyclodextrin.

[7] The pharmaceutical composition of claims 1 to 6, wherein the cyclodextrin derivative is 2-hydroxypropyl-β-cyclodextrin.

[8] The pharmaceutical composition of claims 1 to 7, wherein the composition further comprises a pharmaceutically acceptable additive.

[9] The pharmaceutical composition of claim 8, wherein the pharmaceutically acceptable additive is selected from the group consisting of diluents, pH controllers, osmotic controller, buffers, flavors, binders, thickeners, lubricants, preservatives, and a combination thereof.

[10] The pharmaceutical composition of any one of claims 1 to 9, which comprises a solution containing an inclusion complex prepared by dissolving the thiourea derivative or the pharmaceutically acceptable salt thereof and cyclodextrin or its derivative in water or a buffer.

[11] The pharmaceutical composition of any one of claims 1 to 9, which comprises a solid inclusion complex prepared by dissolving the thiourea derivative or the pharmaceutically acceptable salt thereof and the cyclodextrin or its derivative in water or a buffer, and subjecting the resulting solution to lyophilization, spray drying, vacuum drying or fluid bed drying to remove water.

[12] The pharmaceutical composition of any one of claims 1 to 9, which comprises a solid inclusion complex and/or a solid dispersion prepared by dissolving the thiourea derivative or the pharmaceutically acceptable salt thereof and the cyclodextrin or its derivative in an organic solvent, and subjecting the resulting solution to lyophilization, spray drying, vacuum drying or fluid bed drying to remove the organic solvent.

[13] The pharmaceutical composition of claim 12, wherein the organic solvent is ethanol.

[14] A pharmaceutical formulation comprising the pharmaceutical composition of any one of claims 1 to 13 comprising a thiourea derivative of formula (I) in an amount being effective for preventing or treating a disease selected from the group consisting of pain, acute pain, chronic pain, neuropathic pain, post-operative pain, migraine, arthralgia, neuropathies, nerve injury, diabetic neuropathy, neurodegeneration, neurotic skin disorder, stroke, urinary bladder hypersensitiveness, irritable bowel syndrome, asthma, chronic obstructive pulmonary disease, irritation of skin, eye or mucous membrane, fervescence,

stomach-duodenal ulcer, and inflammatory diseases.

[15] The pharmaceutical formulation of any one of claims 1 to 14, which is an oral formulation selected from the group consisting of a tablet, pill, powder, granule, solution, suspension, syrup and capsule.

[16] The pharmaceutical formulation of any one of claims 1 to 14, which is an injectable solution for intravenous, subcutaneous or intramuscular injection.

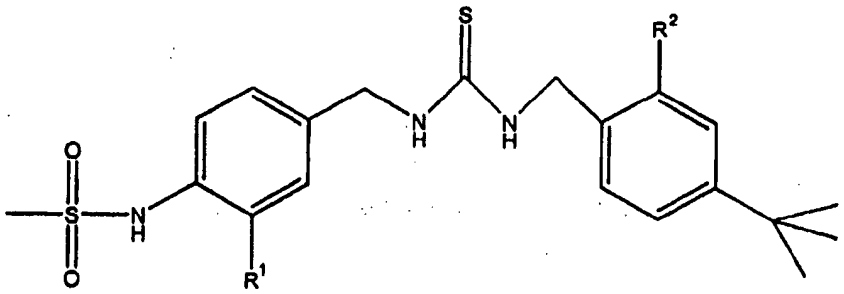
[17] The pharmaceutical formulation of any one of claims 1 to 14, which is a transdermal formulation selected from the group consisting of ointment, cream, lotion, solution, gel, paste, patch and aerosol.

[18] The pharmaceutical formulation of any one of claims 1 to 14, which is a liquid transocular formulation.

[19] The pharmaceutical formulation of any one of claims 1 to 14, which is a liquid or powder-type transnasal formulation.

[20] The pharmaceutical formulation of any one of claims 1 to 14, which is a liquid or semi-solid intravaginal or intrarectal formulation.

[21] Inclusion complex comprising a thiourea derivative of formula (I)



formula (I)

or a pharmaceutically acceptable salt thereof, and a cyclodextrin or its derivative, wherein,

R^1 is hydrogen, fluoro, chloro, methoxycarbonyl, carboxyl or hydroxyaminocarbonyl, and

R^2 is hydrogen, methoxy, ethoxy, propoxy, butoxy, isopropoxy, isobutoxy, neopentoxy, methoxymethoxy or benzyloxy.

[22] The inclusion complex of claim 21, wherein the thiourea derivative is selected from the group consisting of:

1-(4-t-butylbenzyl)-3-(3-fluoro-4-methanesulfonylaminobenzyl)thiourea,

1-(4-t-butylbenzyl)-3-(3-chloro-4-methanesulfonylaminobenzyl)thiourea,

1-(4-t-butylbenzyl)-3-(3-methoxycarbonyl-4-methanesulfonyl-aminobenzyl)thio

urea,

1-(4-t-butylbenzyl)-3-(4-methanesulfonylaminobenzyl)thiourea, and

1-(4-t-butyl-2-isobutoxybenzyl)-3-(4-methanesulfonylaminobenzyl) thiourea.

[23] The inclusion complex of claim 21, wherein the thiourea derivative is 1-(4-t-butylbenzyl)-3-(3-fluoro-4-methanesulfonylaminobenzyl) thiourea.

[24] The inclusion complex of any one of claims 21 to 23, which comprises the cyclodextrin or its derivative in an amount ranging from 1 to 20 parts by weight per 1 part of the thiourea derivative or the pharmaceutically acceptable salt thereof.

[25] The inclusion complex of any one of claims 21 to 24, wherein the cyclodextrin is of α-, β- or γ-type.

[26] The inclusion complex of any one of claims 21 to 25, wherein the cyclodextrin derivative is selected from the group consisting of 2,6-dimethyl-β-cyclodextrin, 2-hydroxyethyl-β-cyclodextrin, 2-hydroxypropyl-β-cyclodextrin, 2-hydroxyethyl-γ-cyclodextrin, 2-hydroxypropyl-γ-cyclodextrin, (2-carboxymethoxy)propyl-β-cyclodextrin, and sulfobutylether-7-β-cyclodextrin.

[27] The inclusion complex of any one of claims 21 to 26, wherein the cyclodextrin derivative is 2-hydroxypropyl-β-cyclodextrin.

[28] Use of an inclusion complex according to any one of claims 21 to 27 for the preparation of a medicament for treating a disease associated with the pathological stimulation and/or increased expression of VR1 receptors.

[29] Use of an inclusion complex according to any one of claims 21 to 27 for the preparation of a medicament for treating a disease selected from the group consisting of pain, acute pain, chronic pain, neuropathic pain, post-operative pain, migraine, arthralgia, neuropathies, nerve injury, diabetic neuropathy, neurodegeneration, neurotic skin disorder, stroke, urinary bladder hypersensitiveness, irritable bowel syndrome, asthma, chronic obstructive pulmonary disease, irritation of skin, eye or mucous membrane, fervescence, stomach-duodenal ulcer, and inflammatory diseases.

[30] Use of an inclusion complex according to claim 29, wherein the disease is pain.

[31] Method of treating a mammal including man suffering from the pathological stimulation of VR1 receptors comprising administering to said mammal a pharmaceutical composition according to any one of claims 1 to 9.

[32] Method according to claim 31, wherein the pathological stimulation of VR1 receptors is associated with at least one of the diseases selected from pain, acute pain, chronic pain, neuropathic pain, post-operative pain, migraine, arthralgia,

neuropathies, nerve injury, diabetic neuropathy, neurodegeneration, neurotic skin disorder, stroke, urinary bladder hypersensitiveness, irritable bowel syndrome, asthma, chronic obstructive pulmonary disease, irritation of skin, eye or mucous membrane, fervescence, stomach-duodenal ulcer, and inflammatory diseases.

[33] Use of a pharmaceutical composition according to any one of claims 1 to 13 for the preparation of a medicament for treating a disease associated with the pathological stimulation and/or increased expression of VR1 receptors.

[34] Use of a pharmaceutical composition according to any one of claims 1 to 13 for the preparation of a medicament for treating a disease selected from the group consisting of pain, acute pain, chronic pain, neuropathic pain, post-operative pain, migraine, arthralgia, neuropathies, nerve injury, diabetic neuropathy, neurodegeneration, neurotic skin disorder, stroke, urinary bladder hypersensitiveness, irritable bowel syndrome, asthma, chronic obstructive pulmonary disease, irritation of skin, eye or mucous membrane, fervescence, stomach-duodenal ulcer, and inflammatory diseases.

[35] Use of a pharmaceutical composition according to claim 34, wherein the disease is pain.